REMARKS

Claims 1, 4-8, 12-18, and 21-24 remain pending. Independent claims 1, 12, and 18 have been amended to include a description of a function of the intermediate coating. The amendments are in accord with teachings throughout the specification, e.g., the discussion at page 7, lines 18-23.

All of the claims stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by a combination of teachings from European Patent Application Publication No. 0094116 A2 of The Procter & Gamble Company ("Close") and U.S. Patent No. 4,804,669 ("Lassen"). Applicants request reconsideration of the rejection, in view of the following discussion.

The present invention, as defined by claim 1, is a solid dosage form having a core comprising an acid-sensitive antidepressant drug, the core being sub-coated with a composition comprising an amino group-containing substance that reacts with acids, and an acidic group-containing enteric coating over the sub-coating. The specification describes the drugs as having functional groups, such as amino groups, that can react in the solid state with the acidic groups present in the enteric coating; the presence of an acid-reactive sub-coating prevents reactions between the drug and enteric coating, thereby improving drug stability during storage of the dosage form.

The antidepressant drugs, such as those listed in the second paragraph on page 6 of the specification, have amino nitrogen atoms, and therefore are considered to be capable of reacting with acidic groups. For example, duloxetine is described in U.S. Patent 5,508,276 to Anderson et al., at column 1, lines 29-42:

> Early dosage form and clinical development of duloxetine showed that it is advisable to formulate it in an enteric form, due to the stability characteristics of duloxetine in acidic solutions, that a pellet formulation was more desirable than a tablet, based on bioavailability studies which showed more consistent plasma profiles were obtained after pellet administration, and that certain difficulties arose in preparing conventional enteric formulations.
>
> Most importantly, duloxetine was found to react with many enteric coatings to form a slowly- or even insoluble coating. Because of this unexpected cross-reactivity, formulations in pellet form were found to have a

> disadvantageous drug-releasing profile and low bioavailability.

For this reason, duloxetine formulations were prepared in Anderson et al. by coating an inert bead with a duloxetine compound, applying a separating layer of an aqueous polymer solution, optionally containing a powdered filler excipient such as talc or silica, then applying the enteric coating. The filler was used to help provide a smooth surface, making the enteric coating more uniform.

The Close publication does not relate to either antidepressant drug dosage forms or to drug-enteric coating chemical interactions. Each active drug compound described by Close is acidic in nature, i.e., has at least one –COOH group. Therefore, Applicants submit that these drugs would not be likely to react with an acidic enteric coating polymer in the solid state. The statement on page 4 of the Office Action that the Close "active core is taught as being selected from a plurality of active agents, all of which have some sensitivity to acid" appears to be scientifically incorrect. If this rejection is maintained, Applicants request that specific factual evidence in support of this basis for the rejection be provided.

Moreover, the Close teachings regarding its compositions have not been correctly characterized in the Office Action. Close described dosage forms that have:

1) cores containing a nonsteroidal analgesic;

2) a first coating over the cores containing an analgesic, preferably the same one as is present in the core, plus a dispersing aid; and

3) an outer enteric coating over the cores.

The purpose of the first coating is to promote particle disintegration in the intestines, by aiding in disrupting the enteric coating (see page 5, lines 15-16). The presence of analgesic drug in the first coating, together with the dispersing aid, would not prevent direct contact between the drug compound and the outer enteric coating, thus rendering the compositions of Close unsuitable for use in the Applicants' invention.

According to the Office Action, combining the teachings of the Lassen patent with Close "cures" the deficiencies of Close. However, this is not the case. The Lassen teachings are confined to the treatment of pain by administering the piperidine compound, paroxetine. According to the patent, the drug can be formulated in <u>any</u> manner, for oral, rectal, topical, or parenteral administration. No specific paroxetine

formulations are disclosed, and the examples describe only administration subcutaneously or orally. It is stated that tablets containing paroxetine may have an enteric coating, but there is no mention of any special formulation parameters or issues. There is nothing in Lassen that would lead someone skilled in the art to modify the teachings of Close, and arrive at the Applicants' claimed compositions.

Lassen does not allude to any problems that exist with enteric coated paroxetine compositions, and Close does not relate to any acid-reactive drug compounds such as paroxetine. Therefore, why would one skilled in the art be motivated to combine the respective teachings? Motivation to combine includes a reasonable expectation of success and, absent recognition of some common problem to be solved, such expectation cannot be present. Applicants submit that simply extracting a mention of the drug paroxetine from Lassen and dropping it into the Close teachings does not establish a legally sufficient *prima facie* case for obviousness. As stated in M.P.E.P. § 2143.01:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless ** the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007).

Further, substituting paroxetine for the drugs disclosed by Close will not yield the presently claimed invention. Close is not attempting to stabilize a reactive drug substance, but has the objective of improving the release of a gastric-irritating drug after a dosage form has passed into the intestines. To accomplish this objective, Close places a portion of the drug into the first coating, along with a substance that enhances disintegration of the enteric coating. Applicants' invention cannot be obtained by simply substituting different drug substances into the products of Close.

In view of the foregoing discussion, Applicants submit that their claims are not rendered unpatentable by the asserted combination of teachings from Close and Lassen. Accordingly, withdrawal of the rejection and allowance of all of claims 1, 4-8, 12-18, and 21-24 are appropriate, and this action is respectfully solicited.

If any matters remain to be resolved before allowance, and a personal or telephonic interview could be useful, please contact the undersigned by telephone to expedite the resolution.

Respectfully submitted,

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